Theoretical and Numerical Study of Cardiac Electrophysiology Problems at the Microscopic Scale.

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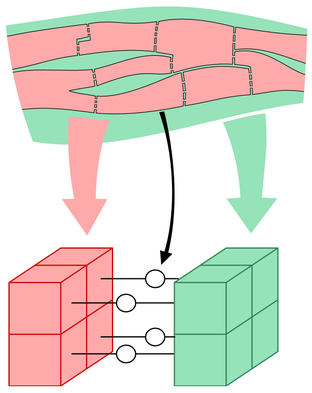
Summary

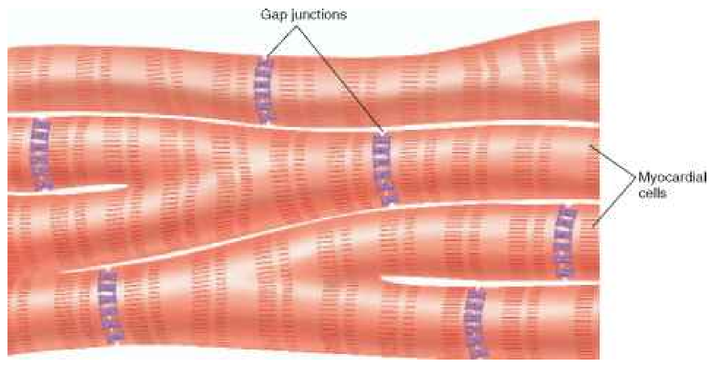
We present a microscopic scale model for the propagation of electric waves in human ventricle cells. We achieved a mathematical analysis of this model and show the existence of a weak solution.

Context

- Modeling studies of cardiac electrophysiology essentially rely on homogenized models like monodomain and bidomain models [**?**];
- Homogenized models cannot take microscopic alterations into account, and cannot represent the nonlinear behaviour of gap junctions between the cells;
- Heart tissue cells constitute a network of cells connected via these gap junctions (see figure), which behave as ionic channels, but between two cells instead of one cell and the extracellular medium.



(a) Cells as a network

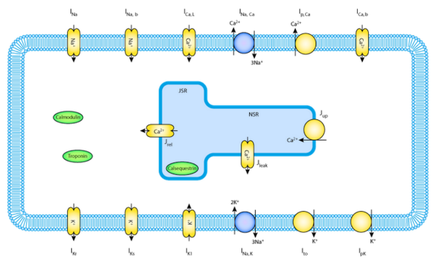


(b) Gap junctions highlight

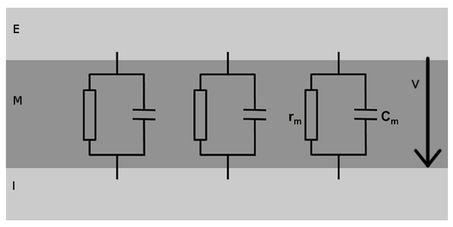
- Dimensions for one cell: length: 175 μm, width: 20 μm, membrane thickness: 10 nm, spacing between neighbours: 1 nm. This leads to experimental and computational challenges;
- Malfunctions and inhomogeneities in heart tissue may lead to alterations in the wave propagation [**?**];
- Microscopic cardiac conduction has been studied experimentally [**?**] and numerically [**?**, **?**], but numerical studies have been limited to simplified 2-dimensional monodomain models.

Purpose

- Develop a new 3-dimensional, structurally realistic model formulation with separate intracellular and extracellular domains.
- Get a better understanding of the consequences of microscopic alterations in the heart;
- Simulate the model efficiently, via domain decomposition methods.



(a) Cell model (Ten Tusscher, Noble, Noble, Panfilov – 2004)

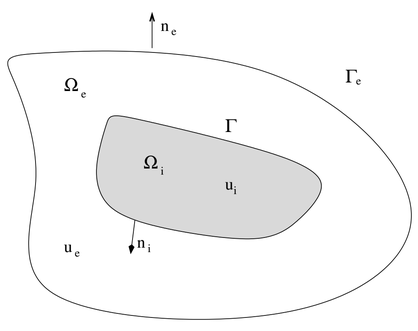


(b) Ionic channels as circuits

A first microscopic mathematical model

Model

We study the problem on a finite time interval $[0;T]$ at the cellular scale using the following sketch



σ_i and σ_e are respectively intracellular and extracellular conductivity. $u_\mathrm{i}, u_\mathrm{e}$ intracellular/extracellular potential. I_ion is the ionic current per unit of membrane area. c_m is the electrical capacitance of the membrane per unit of area. With $v := u_i - u_e$, the model reads

$$\begin{cases} -\nabla \cdot (\sigma_j \nabla u_j) = 0 \text{ in } [0;T] \times \Omega_j, \text{ with } j = i, e \\ \sigma_e \nabla u_\mathrm{e} \cdot n_e = 0 \text{ on } [0;T] \times \Gamma_\mathrm{e}, \\ -\sigma_\mathrm{i} \nabla u_\mathrm{i} \cdot n_\mathrm{i} = \sigma_e \nabla u_\mathrm{e} \cdot n_\mathrm{e} \text{ on } [0;T] \times \Gamma, \\ \qquad = c_m \partial_t v + I_\mathrm{ion}(v,w) \text{ on } [0;T] \times \Gamma. \\ v(0,x) = v_0(x) \text{ on } \Gamma \end{cases} \tag{1}$$

This model presents specific issues

- The ionic term I_ion is nonlinear, and also depends on gating variables;
- The boundary coupling conditions on the membrane include a time derivative, which is not proven to be defined.

Analysis of the microscopic model

Hypotheses

- Conductivity tensors σ_i and σ_e are uniformly continuous and coercive

$$\exists m_j, M_j > 0,\ \forall (x,y) \in \mathbb{R}^3,\ m_j \|y\|^2 < (\sigma_j(x)y, y) < M_j \|y\|^2 \text{ for } j = i, e;$$

- I_ion is Lipschitz-continuous with coefficient λ and $I_\mathrm{ion}(0) = 0$.

Weak problem and main result

There exists a solution $(u_\mathrm{i}, u_\mathrm{e}) \in \mathrm{L}^2([0;T]; \mathrm{H}^1(\Omega_\mathrm{i})) \times \mathrm{L}^2([0;T]; \mathrm{H}^1(\Omega_\mathrm{e}))$ of

$$\begin{aligned} \int_0^T \int_{\Omega_\mathrm{i}} \sigma_\mathrm{i} \nabla u_\mathrm{i} \cdot \nabla \varphi_\mathrm{i} \mathrm{d}x\ \mathrm{d}t + \int_0^T \int_{\Omega_\mathrm{e}} \sigma_\mathrm{e} \nabla u_\mathrm{e} \cdot \nabla \varphi_\mathrm{e} \mathrm{d}x\ \mathrm{d}t + \int_\Gamma c_m v_0 \tilde{\varphi}(t=0) \mathrm{d}x \\ - \int_0^T \int_\Gamma c_m v \partial_t \tilde{\varphi} \mathrm{d}x\ \mathrm{d}t + \int_0^T \int_\Gamma I_\mathrm{ion}(v) \tilde{\varphi} \mathrm{d}x\ \mathrm{d}t = 0. \end{aligned} \tag{2}$$

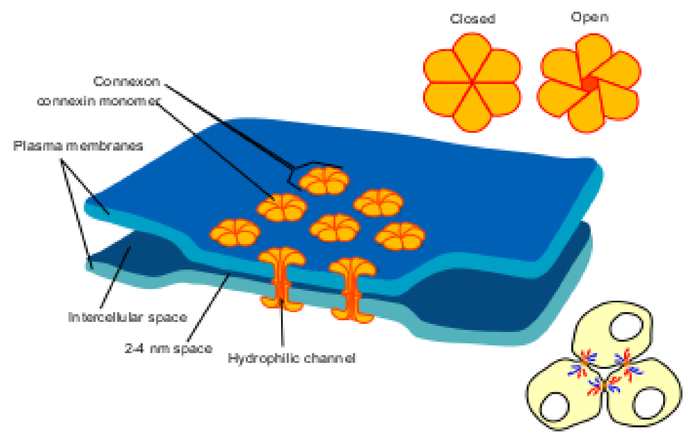
for all $\varphi_j \in L^2(0,T; H^1(\Omega_j))$, $j = i, e$ and $\tilde{\varphi} := (\varphi_i - \varphi_e) \mid_\Gamma \in L^2(0,T; H^{1/2}(\Gamma))$, that is also solution of (1).

Sketch of a proof

- Use a time discretisation for the temporal term $\partial_t v$ on the interface in order to obtain an elliptic problem;
- Use the Lax — Milgram theorem in order to obtain a unique solution;
- Calculate energy estimates especially on time increments of v;
- Via a compacity argument, prove the weak convergence of a time-rebuilt solution;
- Pass to the limit in the rebuilt problem.

Possible model enhancement

A representation of gap junctions (Credit: Mariana Ruiz, 2006) is given in the following figure



Gap junctions have a different conductivity. The penultimate line of equation (1) can be slightly modified on a Gap Junction to take this into account. If we denote Γ_g the set of all gap junctions, it would become

$$-\sigma_{\mathrm{i}1} \nabla u_{\mathrm{i}1} \cdot n_{\mathrm{i}1} = \sigma_g I_g \partial_t v_g + I_g I_{ion}(v) \quad \text{on } \Gamma_g,$$

σ_g being the conductivity of the gap junction, $v_g = u_{i1} - u_{i2}$ the voltage between the two cells at the gap junction, I_g a one or zero operator modelling the open/closed state of the gap junction.

Conclusion and perspectives

Conclusion

- We have designed a basic model and proved existence of a unique solution;
- The hypotheses we made in this regard are consistent with the physics of the problem.

Perspectives

- Model enhancement with gap junctions and specificities of ionic channel (gating variables);
- Ongoing work on simulation, using a homemade framework;
- Enhance the model regarding what happens inside the cells;
- Discuss on the dimensions, especially the thickness of the membrane vs. the spacing between cells.